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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/501,259

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Shunichi Shiozawa

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EDWARDS ANGELL PALMER & DODGE LLP

P.O. BOX 55874

BOSTON, MA 02205

EXAMINER

POHNERT, STEVEN C

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/501,259	Applicant(s) SHIOZAWA ET AL.	
	Examiner Steven C. Pohnert	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 February 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 4 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 4 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 07 September 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This action is in response to papers filed 2/13/2007.

This action is directed to amended claim 4 of the instant specification.

The amendment to the specification has brought the drawings and specification into sequence compliance. The objection to the drawings and sequence compliance objections are withdrawn.

The 012 based on Hillman has been withdrawn as the claim has been amended to require the amino acid sequence comprising SEQ ID NO 1, which Hillman does not teach.

This action contains new ground of rejection and necessitated by amendment.

This action is FINAL.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection has been modified in view of the amendment to claim 4.

These factors have been described by the court in *re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in the Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

The nature of the invention and the breadth of the claims:

The claim 4 encompasses a method of evaluating the possibility of onset or onset of rheumatoid arthritis (RA), by detecting whether a gene coding a protein comprising the amino acid sequence of SEQ ID NO 1 is homozygously present in the subject; and evaluating the onset or onset possibility of rheumatoid arthritis in the subject: wherein the step of evaluating comprise determining the possibility of onset of rheumatoid arthritis is increased if the gene is present homozygously in the subject.

Thus the claims broadly encompass evaluating the onset of RA by the determining whether the homozygous presence of “any” nucleic acid that would result in a protein comprising the amino acid sequences of SEQ ID NO 1 is present in a subject and if it is homozygously expressed there is an increased possibility of RA.

The amount of direction or guidance and the Presence and absence of working examples.

The specification teaches the insertion of GGT at positions 805-807 resulting in a glycine being inserted into amino acid position 269 of SEQ ID NO.1 (see page 25, 1st full paragraph). The specification further teaches this insertion is depicted in SEQ ID

NO. 2 (see page 25, line 10). The specification teaches a 3 base deletion (see page 10, line 11).

The specification teaches the homozygous or heterozygous deletion of “GGT” in SEQ ID NO. 2 occurs in 98.5% of subjects with familial history RA, diagnosed with RA (see Figure 4). The specification further teaches 100% subjects with familial history RA, not diagnosed with RA, were homozygous or heterozygous for deletion of “GGT” in SEQ ID 2 (see figure 4). The specification further teaches 98.2% of subjects with sporadic RA were homozygous or heterozygous for the “GGT” deletion. While 100% of the subjects related to those diagnosed with sporadic arthritis have the homozygous or heterozygous “GGT” deletion.

The specification further teaches the patients that homozygously lack the “GGT” deletion (that have GGT at position 805-807) have RA: familial RA (1.5%) and sporadic RA (1.8%). The specification appears to teach patients that homozygously lack the “GGT” deletion (that have GGT at position 805-807) were found only with RA, but the homozygous or heterozygous “GGT” deletion was found both in subject with RA and those without RA.

The specification teaches of 1410 alleles examined, 1296 were not SEQ ID NO1 and 114 were SEQ ID NO1. This suggests that SEQ ID NO 1 is an underrepresented allele in the population studied.

However, the claims are drawn to detecting the presence or absence of nt805Homo. Thus the claims broadly encompass the absence of nt805 HOMO being predictive of the possibility of RA, however the specification teaches in figure 4 that of

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705 total subjects examined, there were 294 with RA and of the 294 with RA only 5 were homozygous for the presence of SEQ ID NO 1. Thus it appears that the absence of detecting a gene that encodes SEQ ID NO1 is not predictably associated with the onset or possibility of onset of RA.

The state of prior art and the predictability or unpredictability of the art:

The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic

polymorphism (abstract).

The level of skill in the art:

The level of skill in the art is deemed to be high.

Quantity of experimentation necessary:

In order to practice the invention as claimed the skilled artisan would first have to determine a gene homozygously coding for a protein comprising the amino acids of SEQ ID No 1 is predictably associated with RA. This would be replete with undue trial and error experimentation as the claims nor specification provide guidance as the effect of the effect of heterozygous presence of SEQ ID No 1 or how the lack of SEQ ID No 1 relates to the onset of RA.

It would be unpredictable to associate the detection of presence of SEQ ID NO 1 with RA as the specification clearly teaches in Figure 4 that SEQ ID NO 1 is found in 109 subjects (totaling 114 alleles), with 35% of the patients being disease free. Further the absence of SEQ ID No 1 is found in 596 subjects of which 223 did have RA. It is clear without statistical analysis the presence or absence of SEQ ID NO1, by itself is not indicative of increased or decreased onset of RA. Further the low frequency of SEQ ID No 1 allele suggests that it is a very rare allele and thus the presence may not be indicative of anything.

Further it would be unpredictable to associate the homozygous absence of a gene encoding a protein with the sequence of SEQ ID NO 1 with an increased possibility of onset of RA, as 700 of the 705 subjects examined were not homozygous for the presence of SEQ ID NO 1. Of the 700 subjects that were not homozygous for

SEQ ID NO 1, almost half (344) do have RA. Thus as half of the subjects without SEQ ID No 1 did have RA, it would be unpredictable to same the homozygous absence of SEQ ID No 1 is associated with either an increased or decreased chance of onset of RA.

Therefore, in light of the breadth of the claims, the lack of guidance in the specification, the high level of unpredictability in the associated technology, the nature of the invention, the negative teachings in the art, and the quantity of unpredictable experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention as claimed.

Response to Arguments

The amendment to the claim has resulted in amending of the above rejection to reflect the new limitations of the claims and removal of arguments to prior language of “presence or absence” and “a gene homozygously coding a protein.” Thus arguments to the old language are moot.

The response filed on 2/13/2008 asserts the specification and information of the 1.132 declaration enable the instant claim. The response specifically directs the arguments to the office action of 4/27/2007 in which the examiner suggested there may be an association and the Declaration under 37 CFR 1.132. The response specifically asserts there is a statistical difference presented in the declaration. These arguments have been thoroughly reviewed but are not considered persuasive as the declaration does not teach a statistically significant correlation as the p value is 0.07 and p values of 0.05 or less are considered to be statistically significant. Further the data of the

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declaration suggest the unpredictability of the association. Specifically the data of the specification teaches 4 patients out of 225 were homozygous for the insertion with sporadic RA had the mutation and none of the 383 controls had the homozygous insertion, however, the declaration teaches 33 of 115 patients had the homozygous insertion while 15 of the 85 controls were homozygous. First as previously noted, the declaration's data is not statistically significant. Second, the wide variation in the data suggests unpredictability, different populations, etc. An allele or mutation that is found in 0.066% (4 of 608 in sporadic group of specification) of a population would not predictably be found in over 24% (48 of 200 in declaration data). Further the specification teaches at least 71% of subjects in each group studied homozygously lacked the insertion or 84.5%. The declaration teaches 15 of 200 (7.5%) of the subjects studied were homozygous. Thus as the data of the declaration suggests a trend toward statistical significance, to is not consistent with the data of the specification. The data of the specification suggests the insertion may be an under represented allele, while the declaration suggests the lack of the insertion is under represented. Together the specification and declaration suggest the mutation is unpredictable.

The response further asserts that Hirshhorn and Ioannides suggest association data is not reproducible and the data of the declaration and specification are reproducible. As addressed in the office action of 11/13/2007 the response to arguments on pages 10-11, point out the inconsistencies between the data of the specification and the declaration that have been analyzed further above. Thus in view

of these discrepancies in the data and the teachings of Hirshhorn and Ioannides, the artisan would view the data as unpredictable.

Thus the Enablement rejection has been modified and maintained.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claim 4 is rejected under 35 U.S.C. 102(b) as being anticipated by Davis et al (WO96/11269 published April 18, 1996).

The MPEP 2111 teaches:

During patent examination, the pending claims must be “given their broadest reasonable interpretation consistent with the specification.” >The Federal Circuit’s en banc decision in Phillips v. AWH Corp., 415 F.3d 1303, 75 USPQ2d 1321 (Fed. Cir. 2005) expressly recognized that the USPTO employs the “broadest reasonable interpretation”.

The amended claim requires detecting a whether a gene encoding a protein of SEQ ID NO 1 is homozygously present and the gene is homozygously present evaluating the onset of rheumatoid arthritis is increased. Thus the claim has a single active step of detecting SEQ ID NO 1 and the homozygosity and evaluation steps are conditional only on the presence of homozygous detection.

With respect to claim 4, Davis et al teaches

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Db 850 ACAAATGAAATCTTGAAGATCCATGAAAAAACAGTTTATTAGAACATAAAATCTTAGAA
909

Qy 201 MetGluGlyLysHisLysGluGluLeuAspThrLeuLysGluGluLysGluAsnLeuGln
220
|||||

Db 910 ATGGAAGGAAAACACAAGGAAGAGTTGGACACCTTAAAGGAAGAGAAAGAGAACCTTCAA
969

Qy 221 GlyLeuValThrArgGlnThrTyrIleIleGlnGluLeuGluLysGlnLeuAsnArgAla
240
|||||

Db 970 GGCTTGGTTACTCGTCAAACATATATAATCCAGGAGCTGGAAAAGCAATTAAACAGAGCT
1029

Qy 241 ThrThrAsnAsnSerValLeuGlnLysGlnGlnLeuGluLeuMetAspThrValHisAsn
260
|||||

Db 1030 ACCACCAACAACAGTGTCTTCAGAAGCAGCAACTGGAGCTGATGGACACAGTCCACAAC
1089

Qy 261 LeuValAsnLeuCysThrLysGluGlyValLeuLeuLysGlyGlyLysArgGluGluGlu
280
|||||

Db 1090 CTTGTCAATCTTTGCACTAAAGAAGGTGTTTTACTAAAGGGAGGAAAAAGAGAGGAAGAG
1149

Qy 281 LysProPheArgAspCysAlaAspValTyrGlnAlaGlyPheAsnLysSerGlyIleTyr
300
|||||

Db 1150 AAACCATTTAGAGACTGTGCAGATGTATATCAAGCTGGTTTTAATAAAAGTGAATCTAC
1209

Qy 301 ThrIleTyrIleAsnAsnMetProGluProLysLysValPheCysAsnMetAspValAsn
320
|||||

Db 1210 ACTATTTATATTAATAATATGCCAGAACCCAAAAGGTGTTTTGCAATATGGATGTCAAT
1269

Qy 321 GlyGlyGlyTrpThrValIleGlnHisArgGluAspGlySerLeuAspPheGlnArgGly
340
|||||

Db 1270 GGGGGAGGTTGGACTGTAATACAACATCGTGAAGATGGAAGTCTAGATTTCCAAAGAGGC
1329

Qy 341 TrpLysGluTyrLysMetGlyPheGlyAsnProSerGlyGluTyrTrpLeuGlyAsnGlu
360
|||||

Db 1330 TGGAAGGAATATAAAATGGGTTTTGGAAATCCCTCCGGTGAATATTGGCTGGGGAATGAG
1389

Qy 361 PheIlePheAlaIleThrSerGlnArgGlnTyrMetLeuArgIleGluLeuMetAspTrp
380
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Db      1390 TTTATTTTGGCCATTACCAGTCAGAGGCAGTACATGCTAAGAATTGAGTTAATGGACTGG
1449

Qy      381 GluGlyAsnArgAlaTyrSerGlnTyrAspArgPheHisIleGlyAsnGluLysGlnAsn
400
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      1450 GAAGGGAACCGAGCCTATTACAGTATGACAGATTCCACATAGGAAATGAAAAGCAAAAC
1509

Qy      401 TyrArgLeuTyrLeuLysGlyHisThrGlyThrAlaGlyLysGlnSerSerLeuIleLeu
420
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      1510 TATAGGTTGTATTTAAAGGTCACACTGGGACAGCAGGAAAACAGAGCAGCCTGATCTTA
1569

Qy      421 HisGlyAlaAspPheSerThrLysAspAlaAspAsnAspAsnCysMetCysLysCysAla
440
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      1570 CACGGTGCTGATTTTCAGCACTAAAGATGCTGATAATGACAACTGTATGTGCAAATGTGCC
1629

Qy      441 LeuMetLeuThrGlyGlyTrpTrpPheAspAlaCysGlyProSerAsnLeuAsnGlyMet
460
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      1630 CTCATGTTAACAGGAGGATGGTGGTTTGATGCTTGTGGCCCTCCAATCTAAATGGAATG
1689

Qy      461 PheTyrThrAlaGlyGlnAsnHisGlyLysLeuAsnGlyIleLysTrpHisTyrPheLys
480
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      1690 TTCTATACTGCGGGACAAAACCATGGAAACTGAATGGGATAAAGTGGCACTACTTCAAA
1749

Qy      481 GlyProSerTyrSerLeuArgSerThrThrMetMetIleArgProLeuAspPhe 498
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      1750 GGGCCCAGTTACTCCTTACGTTCCACAACCTATGATGATTGACCTTTAGATTTT 1803

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.The sequence of Davis is nucleic acid encoding SEQ ID NO 1 of the instant specification. Davis teaches detection of the presence of the nucleic acid in a cell (see page 31, lines 20-25). Davis teaches this sequence was isolated from humans (see page 9, lines 21-25 and page 44).

Davis et al thus teaches all the required steps of the newly amended claim.

4. Claim 4 is rejected under 35 U.S.C. 102(a) as being anticipated by Shiozawa et al (Nippon Rinsho (2002) volume 60, pages 2269-2275)(translation pages 1-19).

The MPEP 2111 teaches:

During patent examination, the pending claims must be “given their broadest reasonable interpretation consistent with the specification.” >The Federal Circuit’s en banc decision in Phillips v. AWH Corp., 415 F.3d 1303, 75 USPQ2d 1321 (Fed. Cir. 2005) expressly recognized that the USPTO employs the “broadest reasonable interpretation”.

The amended claim requires detecting a whether a gene encoding a protein of SEQ ID NO 1 is homozygously present and the gene is homozygously present evaluating the onset of rheumatoid arthritis is increased. Thus the claim has a single active step of detecting SEQ ID NO 1 and the homozygosity and evaluation steps are conditional only on the presence of homozygous detection.

Shiozawa et al teaches on page 15 of the RA2 gene (angiopoietin-1) was found with the gly 269 insertion (SEQ ID NO 1) in 83/335 of RA patients, while in only 30 of 383 control patients. Shiozawa et al thus teaches a method of detecting SEQ ID NO 1 and evaluating the onset of RA.

Response to arguments

The response asserts that the art of Shiozawa is not available under 102 (a) as Shiozawa is the current inventor. This argument have been thoroughly reviewed but are not considered persuasive as the applicant has not presented an affidavit or declaration under 37 CFR 1.132 showing the reference is not by another, nor has the

applicant provided a translation to demonstrate that JP2002-005326 is enabling for the instant claim.

The response further asserts that Shiozawa does not anticipate the instant claims as the art does not teach the conditional steps of determining whether the sequence is homozygously overexpressed and if the sequence is homozygously overexpressed determining the subject has increased possibility of rheumatoid arthritis onset. These arguments have been thoroughly reviewed but are not considered persuasive as the steps are conditional and only required if the nucleic acid is determined to be expressed homozygously.

Summary

No claims are allowed.

Conclusion

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

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the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is 571-272-3803. The examiner can normally be reached on Monday-Friday 6:30-4:00, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Steven Pohnert

/Sarae Bausch/
Primary Examiner, Art Unit 1634